REMARKS

Claims 1-4, 8, 11-13, 15-18, and 22 have been amended for clarity. In addition, non-elected claims 23-31 have been cancelled to advance the prosecution of this application.

In the Office Action of April 20, 2006, the Examiner rejected claims 1-7, 15, 16, 18-20, and 22 under 35 U.S.C. §102(b) for being anticipated by U.S. Patent No. 6,270,802 to Thanoo et al. (hereafter Thanoo). Claims 8-14, 17, and 21 were rejected under 35 U.S.C. §103(a) for being obvious over Thanoo.

The present invention relates to a method for the preparation of microspheres, which comprises the following steps:

(a) emulsifying a medicament-containing polymer solution containing a medicament, a biocompatible and biodegradable hardly-water-soluble polymer and an organic solvent having a boiling point lower than that of water into an aqueous solution in an emulsifying device to form an emulsion wherein said medicament-containing polymer solution is dispersed in the aqueous solution;

(b) transferring the obtained emulsion into a microsphere storage tank;

(c) introducing a part of the emulsion from the microsphere storage tank into a cross flow filter;

(d-1(-i) returning a liquid passing over the cross flow filter to the microsphere storage tank;

(d-1)-ii) recycling a filtrate filtered from the above cross flow filter as an aqueous solution for step (a), repeating steps (a) to (d-1), and when the organic solvent having a boiling point lower than that of water is immiscible with water, then evaporating said organic solvent in the microsphere storage tank during this circulation process; or

(d-2)-i) returning a liquid passing over the cross flow filter to the microsphere storage tank;

(d-2)-ii) discharging a filtrate filtered from the above cross flow filter without recycling it as the aqueous solution for step (a), repeating steps (a) to (d-2) using a fresh aqueous solution, and when the organic solvent having a boiling point lower than that of water is immiscible with water, then evaporating said organic solvent in the microsphere storage tank during this circulation process; and

(e) collecting microspheres in the microsphere storage tank after step (d-1) or step (d-2) is completed.

According to the method of the present invention, the aqueous solution can only be effectively separated from the emulsion prepared in the emulsifying device and transferred into a microsphere storage tank by means of the cross flow filter. Hence, even if the emulsion producing process is repeated, the emulsion in the microsphere storage tank can be kept at a constant volume. Accordingly, this process permits a downsizing of the apparatus, inhibition of contamination of bacteria and further airtight closing of an apparatus whereby it is effective for inhibiting evaporation of organic solvent which causes environmental problems.

Besides, according to the method of the present invention, even when a large amount of microspheres are produced, the emulsifying scale at one time can be made small, and hence, homogeneous emulsification can easily be done, and thereby high quality microspheres can be obtained.

Moreover, according to the present method, even in a single apparatus for producing microspheres, the microsphere production scale at one time can be easily controlled by varying the emulsifying frequency.

Thanoo is concerned with a method for formulating a plurality of active agent containing polymer bodies by:

(a) providing a suspension of active agent containing polymer bodies in a continuous phase in a process vessel;

(b) while maintaining the polymer bodies in suspension, replacing the continuous phase with a formulating medium by moving the suspension through a filter adapted to remove the continuous phase and returning the polymer bodies as a suspension to the process vessel; and

(c) removing the suspension of active agent containing polymer bodies and formulating medium from the process vessel.

According to this method, the active agent containing polymer bodies are formulated in a state of suspension, so that production losses are inhibited (col. 2, lines 30-36). Advantages of this method are that it provides a simple, economic, efficient and aseptic means of formulating a product (col. 1, lines 60-63).

Polymer bodies is a generic term that includes microspheres and microcapsules (col. 1, lines 53-56 and col. 2, lines 37-40). Further, it is understood that to "formulate" means to process the microspheres into a final product in view of the description of "a process that can efficiently, economically and aseptically process and formulate microcapsules and microspheres into final dosage forms." (col. 1, lines 48-50) and "in a

suitable pharmaceutically acceptable diluent or carrier, i.e., formulating medium" (col. 2, lines 45-49).

Thus, the invention of Thanoo is concerned with a formulation process of already prepared microspheres or the like, wherein a filter is used in the formulation process. In other words, it would be a process that could be performed on microspheres made by applicants' process. Thus it is submitted that the Examiner has misunderstood the reference in equating the process vessel used in the formulation process of Thanoo to the microsphere storage tank used in the present invention. The process vessel of Thanoo is used for the purpose of storing formulated microspheres in the final dosage form, whereas the microsphere storage tank in the present invention is used for the purpose of storing microspheres prepared by the claimed process.

It is noted that there is disclosed in Thanoo, in steps (a) to (e) of claims 16 and 19, for example, a process for forming the microspheres. In this process a substance, before forming the active agent containing polymer bodies or microspheres by removing the solvent, is in the form of an emulsion. However, this is not the suspension that is prepared after forming the polymer bodies. Moreover, there is no disclosure of this emulsion ever being passed through a filter as claimed.

In Example 2, two process vessels having a larger size and a smaller size are used, wherein microspheres are produced and formulated using the apparatus shown in Fig. 4. In Fig. 4, the vessel 316 serves as both a solvent removal vessel and a processing vessel for concentrating and washing (col. 10, lines 53-55). The smaller vessel 416 serves as a processing vessel for formulating the microspheres. The microsphere suspension contained in the vessel 316 flows through a hollow fiber

filter 322, where the continuous phase is removed via the line 332, and the microsphere suspension is returned to the vessel 316. (col. 10, lines 54-66).

Removal of excess solvent from the microspheres is accomplished in the same equipment by continuing the above process while adding wash water solvent and continuing to draw off hollow fiber filter permeate, the volume and concentration of the microsphere suspension remaining constant while the solvent concentration of the suspension fluid is reduced from an initial volume (col. 11, lines 18-29). It is mentioned that the residual solvent level of the microspheres is reduced by carrying out the removal of solvent by raising the temperature of the system (col. 11, lines 30-57). However, these steps are all carried out on the suspension, not the emulsion, and after the microspheres have been formed.

In contrast, the present invention is a process for the preparation of the microspheres using a circulating process where a series of steps (emulsifying to in-water drying steps) are repeated utilizing a cross flow filter. This process has the following features:

(i) It permits downsizing of the apparatus, inhibition of contamination of bacteria and airtight closing of the apparatus, whereby it is effective for inhibiting evaporation of organic solvent which causes environmental problems.

(ii) The emulsifying scale at one time can be made small, and hence, homogeneous emulsification can easily be done, and thereby microspheres of high quality can be obtained.

(iii) Even in a single apparatus for producing microspheres, the microsphere production scale at one time can be easily controlled.

In summary, Thanoo is concerned with a formulation process of previously prepared microspheres or the like. In this process, a filter is used to a) replace the continuous phase in the suspension of active agent containing polymer bodies with the formulating medium, or (b) replace the continuous phase in the suspension of active agent containing polymer bodies with water, followed by further replacing water with a formulating medium. This is not the method of the present invention where a cross flow filter is used in the step of the preparing the microspheres.

As acknowledged above, Thanoo discloses that a process vessel can serve as a solvent removal vessel and removal of solvent from the microspheres and concentration and washing of the microspheres can be done in the vessel, and that a microsphere suspension flows through a hollow fiber filter in the process where a continuous phase permeating the hollow fiber filter is removed, and the suspension passing through the filter is returned to the vessel. However, the hollow fiber filter is merely used in the step of removal of solvent from already prepared microspheres. It is not used, nor does the reference suggest using the filter in the circulation process of the present invention, i.e., the claimed emulsifying step to the in-water drying step, or the advantages (i), (ii) and (iii) that result from such process.

Accordingly, it is submitted that claim 1 cannot be considered to be anticipated by Thanoo, and its withdrawal as a ground of rejection of claim 1 under §102(b) is requested. Since all of claims 2-22 depend from claim 1, it is submitted that these claims are patentable over the cited reference for the same reasons both under §102(b) and §103(a).

It is believed claims 1-22 are in condition for allowance.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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